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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/600,007	06/18/2003	Martin Stanton	23239-531	6058

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EXAMINER	
ASHEN, JON BENJAMIN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 03/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/600,007	STANTON ET AL.	
	Examiner	Art Unit	
	Jon B. Ashen	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *3,5,7 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/04; 8/04; 12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1, 2, 4, 6 and 8 and the species, small molecule chemotherapeutic, in the reply filed on 12/15/05 is acknowledged.

Status of the Application

2. Claims 1-9 are pending in this application. Claims 3, 5, 7 and 9 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Election was made **without** traverse in the reply filed on 12/15/05.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 8 is broadly drawn and reads on a large genus of aptamer-toxin conjugates that are required to provide a therapy, *in vivo*, wherein the aptamer toxin

conjugates comprise an aptamer targeting moiety and a cytotoxic moiety that are conjugated by a non-covalent bond. The claims read broadly on aptamer-toxin conjugate therapeutics that are conjugated (i.e., joined) joined by any non-covalent bonds including hydrogen bonds, Van der Walls interactions, ionic bonds, at least.

However, the specification as filed does not provide an adequate written description of the broad genus of the claimed therapeutic conjugates that will function, commensurate wit the breadth of what is claimed, to provide a therapy, *in vivo*.

No definition of non-covalent conjugation and no examples of non-covalent aptamer-toxin conjugates could be located in the specification as filed. The specification does not disclose any treatment, *in vivo*, of any disease or condition of any kind using any aptamer-toxin conjugate therapeutics as claimed. The specification discloses only 4 species of aptamer-toxin conjugates that are all PDGF aptamers that are covalently linked to a radioisotope, a small peptide, a protein and an chemotherapeutic molecule (examples 1-4 respectively). The specification, however, is merely prophetic with regard to aptamer-toxin conjugate therapeutics that are non-covalent conjugates, that will function, commensurate with the breadth of what is claimed, to provide a therapy *in vivo*.

The specification thereby provides a narrow disclosure and a few species of covalently conjugated aptamer-toxin conjugate therapeutics but no adequate written description of the claimed non-covalently conjugated aptamer-conjugates that would indicate that applicant was in possession of the claimed invention. The specification provides no disclosure of the structure of any particular aptamer-conjugates (covalently

or non-covalently conjugated) that corresponds with the function of providing a therapy *in vivo* and no distinguishing identifying characteristics of the claimed non-covalently linked conjugates that would indicate that applicant was in possession of the genus as claimed. Therefore, Applicant has not disclosed a representative number of species from within the broadly claimed genus of non-covalent aptamer-toxin therapeutic conjugates that will provide a therapy, *in vivo*, commensurate with the breadth of what is claimed, that would indicate they were in possession of the claimed invention.

In particular, one of skill cannot envision a representative number of the species of aptamer-toxin conjugates as claimed because the identification of the required aptamer targeting moiety is an unpredictable process, relying on complex 2 and 3 structures for specific molecular binding (as shown by the disclosure of the SELEX process in the instant specification (see [0065]). This is true for the binding of the aptamer, no-covalently, to the cytotoxic moiety and for the binding of the aptamer, non-covalently, to the target molecule (as a targeting moiety). In the instant case, both binding specificities of the claimed non-covalent aptamer toxin conjugate would require empirical discovery; i.e., selection as above, which would be unpredictable. Consequently, one of skill would therefore expect, in the face of this unpredictability, to have to screen for compounds that were functional, commensurate with the breadth of the genus claimed.

The state of the art cannot provide the required written description of the claimed invention because the state of the art recognizes the unpredictability of providing an *in vivo* therapy using nucleic acid therapeutics and is silent with regard to the non-covalent

conjugation of aptamers to toxins, disclosing only covalent attachment of reporter or therapeutic molecules that are shown to provide a therapy *in vivo* (see Tavitian and references therein below for a review of the state of the art in aptamer drug development).

MPEP § 2163[R-2] I. states:

> To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., > Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003);< Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116.
>
> The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., Vas-Cath, Inc., 935 F.2d at 1563-64, 19 USPQ2d at 1117.
>
> Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").
>
> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. > Enzo Biochem, 323 F.3d at 964, 63 USPQ2d at 1613.<

In the instant case, Applicant has not provided adequate written description of their invention because the specification does not convey, with reasonable clarity to those of skill in the art, as of the filing date sought, that applicant was in possession of the invention now claimed. Applicant has not shown how the invention was "ready for

patenting" such as by the disclosure of the structure of a non-covalent conjugate that was an aptamer-toxin conjugate therapeutic that functions *in vivo* to provide a therapy, commensurate with the breadth of what is now claimed (that shows that the claimed invention was complete), or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of a representative number of species from within the broad genus of non-covalent conjugates as claimed.

5. Claims 1, 2, 4, 6 and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

The scope of claims 1, 2, 4, 6 and 8 is broadly drawn and reads on an aptamer-toxin conjugate that is required to provide a therapy, *in vivo*, wherein the aptamer toxin conjugate comprises a targeting moiety that is an aptamer and a cytotoxic moiety that is

a small molecule chemotherapeutic. The scope of the claims reads on any aptamer that targets anything, including proteins, carbohydrates, small molecules, at least, wherein the aptamer is conjugated to a cytotoxic moiety that can be any cytotoxic moiety wherein the function of the claimed conjugate is to provide a therapy, which as claimed can be any therapy for any disease.

The specification as filed, however, does not provide a disclosure which would enable the skilled artisan to make and use the claimed aptamer-toxin conjugate therapeutic agent. The specification provides no examples of any therapy that is provided by any aptamer-toxin conjugate therapeutic agents. The specification discloses 4 species of aptamer conjugate as claimed, that are all PDGF aptamer conjugated to a radioisotope, a small peptide, a protein and an chemotherapeutic molecule (examples 1-4 respectively). The specification, however, is merely prophetic with regard to any therapy that may be provided by the claimed conjugate, providing only a general disclosure of aptamer selection via SELEX, a general discussion of aptamer binding and a general discussion of pharmaceutical compositions comprising and modes of administration of the claimed aptamer-toxin conjugates (see pgs. 8-10, 12-15, 29-33). However, the specification as filed provides no specific guidance with regards to how to make and use aptamer conjugate therapeutics as claimed, such that the skilled artisan could provide a therapeutic effect, *in vivo*, to a subject, using the claimed aptamer conjugat4es.

The state of the art at the time the instant invention was made relative to the enablement of the nucleic acid therapies *in vivo* recognized that there is a high degree

of unpredictability in the art of applying nucleic acid therapeutics (i.e., antisense nucleic acids, ribozymes, interfering RNAs etc) without direct evidence of a specific biological or therapeutic effect due to numerous obstacles that continue, to the present day, to hinder the application of nucleic acid therapies *in vivo* (whole organism). Such obstacles include, for example, problems with delivery (including uptake by cells) and target accessibility (see below: Opalinska et al.).

In regard to the use of nucleic acid therapeutics *in vivo*, Opalinska et al. 2002 (Nature Reviews, Vol. 1, pp. 503-514) provide a review of the challenges that remain before nucleic acid therapy becomes routine in therapeutic settings and clearly indicate that the art of nucleic acid therapy remains highly unpredictable and unreliable, particularly with regards to specific delivery *in vivo*, at an effective concentration to provide a therapeutic effect. According to Opalinska et al., "Although conceptually elegant, the prospect of using nucleic acid molecules for treating human malignancies and other diseases remains tantalizing, but uncertain. The main cause of this uncertainty is the apparent randomness with which these materials modulate the expression of their intended targets. It is a widely held view that molecule delivery, and selection of which messenger RNA sequence to physically target, are core stumbling blocks that hold up progress in the field" (pg 503). Opalinska et al. also note that .. "[I]t is widely appreciated that the ability of nucleic acid molecules to modify gene expression *in vivo* is quite variable and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule

delivery to targeted cells and specific compartments within cells, and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" (pg. 511).

In regards to the use of aptamer-toxin conjugates to provide a therapeutic effect *in vivo*, Tavitian, in 2003 review of aptamers as therapeutic agents and targeting agents for *in vivo* imaging state, "The discrimination and targeting capacities of aptamers suit the exquisitely as imaging agents for non-invasive diagnostic procedures. In this respect, escort aptamers are a budding concept in which the aptamer oligonucleotide may be used to deliver an active drug, radionuclide, toxin or cytotoxic agent to the desired site for diagnostic tests and therapy (Gut, 2003, Vol. 52: pp. 40-47). This review, published the same year as the instant application, clearly indicates that aptamer-conjugates for therapeutic use have potential based on their use as non-invasive imaging agents but remains prophetic with regards to any actual therapy that is or has been provided in the art, pointing out that escort aptamers are a budding concept.

Given the art recognized unpredictability of the application of nucleic acid therapeutics *in vivo* and recognition that aptamer-conjugate therapeutics (i.e., escort aptamers) were a budding concept, at the time the invention was made, the disclosure of the specification does not provide the specific guidance that would have been required, by skilled artisan, to overcome the art recognized obstacles with regards to the provision of a specific treatment effect *in vivo,* using a nucleic acid therapeutic. In order to practice the invention as claimed, the skilled artisan would need, therefore, to perform a vast quantity of undue *de novo* trial and error experimentation in order determine how

to make and use the claimed aptamer-toxin conjugate therapeutics, *in vivo* to provide a treatment. This undue *de novo* trial and error experimentation would have included the determination of such factors as determination of a disease or condition to be treated such that a therapy was provided, determination of dosage, route of administration, kinetics of uptake, disposition of the inhibitors or compounds in cells, tissues or the organism to be treated, and the half-life and stability of the required inhibitors or compounds, *in vivo*. this determination would not have been routine and would have required specific guidance.

Therefore, based on the nature of the invention as a compound that is required to provide a treatment *in vivo*, the degree of unpredictability in the art of nucleic acid and oligonucleotide therapeutics at the time the invention was made, the breadth of the claimed aptamer conjugate, the lack of guidance in the specification as to what particular species of aptamer-conjugate therapeutic as claimed will function to provide any particular therapy, the need to screen multiple species of said aptamer-conjugate therapeutic so as to allow identification of particular species as functional *in vivo* and the quantity of *de novo* trial and error experimentation necessary to discover the above, an undue amount of experimentation would be required in order to make and use the instant invention as claimed.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 2, 4 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Hicke et al. (US 6,232,071; Reference cited on the PTO Form 1449 filed 12/2004). The invention set forth in claims 1, 2, 4 and 6 is drawn to an aptamer-toxin conjugate that comprises a targeting aptamer conjugated to a cytotoxic moiety that is a small molecule chemotherapeutic wherein the targeting moiety and cytotoxic moiety are covalently conjugated.

Hicke et al. disclose aptamer-toxin conjugate therapeutic agents that are used to treat cancer that are tenasicn-C aptamers that are covalently conjugated to cytotoxic moieties including small molecule chemotherapeutics (col. 11).

Therefore, Hicke et al. anticipate the instant invention as set forth in claims 1, 2, 4 and 6.

8. Claims 1, 2, 4 and 6 are rejected under 35 U.S.C. 102(e) as being anticipated by Warren (US 6,610,841; Reference cited on the PTO Form 1449 filed 12/2004). The invention set forth in claims 1, 2, 4 and 6 is relied upon as above.

Warren et al. disclose nucleic acid ligand-prodrugs that are targeting aptamers covalently conjugated to small molecule chemotherapeutics (disclosed as oncolytic molecules) that are used to treat cancer (e.g., leukemia) (col. 15; figures 6-9 and descriptions thereof).

Therefore, Warren anticipates the instant invention as set forth in claims 1, 2, 4 and 6.

9. Claims 1, 2, 4 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Warren (WO 99/30561; Reference cited on the PTO Form 1449 filed 12/2004). The invention set forth in claims 1, 2, 4 and 6 is relied upon as above.

Warren et al. disclose nucleic acid ligand-prodrugs that are targeting aptamers covalently conjugated to small molecule chemotherapeutics (disclosed as oncolytic molecules) that are used to treat cancer (e.g., leukemia) (pg. 22, figures 6-9 and descriptions thereof).

Therefore, Warren anticipates the instant invention as set forth in claims 1, 2, 4 and 6.

Double Patenting

10. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

11. Claims 1, 2, 4, 6 and 8 of this application conflict with claims 1, 2, 4, 6 and 8 of Application No. 10/826,077. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

12. Claims 1, 2, 4, 6 and 8 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 2, 4, 6 and 8 of copending Application No. 10/826,077, This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

13. Claims 1, 2, 4, 6 and 8 are directed to the same invention as that of claims 1, 2, 4, 6 and 8 of commonly assigned 10/826,077. The issue of priority under 35 U.S.C. 102(g) and possibly 35 U.S.C. 102(f) of this single invention must be resolved.

Since the U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300), the assignee is required to state which entity is the prior inventor of the conflicting subject matter. A terminal disclaimer has no effect in this

situation since the basis for refusing more than one patent is priority of invention under 35 U.S.C. 102(f) or (g) and not an extension of monopoly.

Failure to comply with this requirement will result in a holding of abandonment of this application.

Conclusion

14. No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image

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Jba

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER